

REMARKS

In view of the following remarks, the Examiner is requested to withdraw the rejections and allow claims 1, 2, 4-16 and 28, the only claims pending and currently under examination in this application.

Formal Matters

Claim 1 has been amended for clarity. Support can be found in the claim as previously filed. No new matter has been added by way of this amendment and its entry is respectfully requested.

Claim Rejections - 35 USC § 103 Anderson, Schleifer, and Schleifer

Claims 1, 2, 4-15, and 28 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Anderson et al. (US 5186824), in view of Schleifer et al. (A) (US 6077674) or Schleifer et al. (B) (US 6309828). The Applicants respectfully traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. See *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007))). "Subsumed within the Graham factors is a subsidiary requirement articulated by this court that where, as here, all claim limitations are found in a number of prior art references, the burden falls on the challenger of the patent to show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007) citing *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006).

In making this rejection, the Examiner asserts that applying Anderson's rotating processor for separations of phases of different density to the method of making an array from pre-synthesized oligonucleotides disclosed by Schleifer (A) and (B) would render the claimed invention obvious.

The Applicants submit that the cited references are deficient for not teaching or suggesting a method that involves the steps recited in Claim 1. Claim 1 is drawn to an *in situ* fabrication process of an addressable array. The first step of Claim 1 involves contacting blocked nucleoside monomers to at least a first location and a second location of a surface of a substrate to produce a substrate surface displaying covalently bound blocked monomers. After oxidation and displacing of deblocking fluid, the next step, step (e) involves contacting blocked nucleoside monomers to at least said first location and said second location of said substrate surface to produce a substrate surface displaying covalently bound blocked nucleotides. The Applicants contend that the combination of Anderson with either Schleifer (A) or Schleifer (B) does not provide these steps recited in Claim 1.

In attempting to establish this rejection, the Examiner points to column 19, lines 55-58 in Anderson as teaching the claimed invention. The Examiner also asserts that production of an addressable array by polymer synthesis on CPG support followed by cleavage is well-known as disclosed in Schleifer (A) or Schleifer (B).

However, production of addressable array by polymer synthesis on CPG followed by cleavage is not what is recited in Claim 1. Step (a) of Claim 1 specifically recites "contacting blocked nucleoside monomers to at least a first [...] and second locations of a surface of said substrate [...]" to produce a substrate surface displaying covalently bound blocked monomers." To further clarify the *in situ* fabrication process described by Claim 1, step (e) repeats the contacting step to first produce a "substrate surface displaying covalently bound blocked nucleotides" and finally after steps (f), (g), and (h) to produce an "addressable array having a first polymeric ligand at said first location of said substrate and a second polymeric ligand at said second location of said substrate." The passages in Anderson pointed out by the Examiner do not teach the reiteration of these steps to produce an addressable array as claimed by the Applicants. They also do not teach contacting blocked nucleoside monomers to the first and second location of said substrate surface to produce a

substrate surface displaying covalently bound blocked nucleotides, with "said substrate surface" as the substrate surface in step (a). Since Anderson only describes oligonucleotide synthesis on CPG support, there can be no teaching or suggestion of adding blocked monomers twice to the first and second location of the same substrate surface, much less that the substrate surface is the same surface displaying the ligands in the addressable array.

The Applicants further contend that combining Schleifer (A) and Schleifer (B) with Anderson does not suggest the claimed invention. As the Examiner admits, combining the references would result in the production of an addressable array by cleaving off polymers synthesized on CPG and attaching them onto a substrate surface that is different from the surface of the CPG. As explained above, this is not what Claim 1 is claiming. Steps (e), (f), and (g) of Claim 1 clearly states the contacting, oxidation, displacing deblocking fluid steps on a surface of the same substrate as the substrate of the addressable array, with at least a first and a second locations. The substrate of Anderson on which synthesis occurs is not an addressable array with at least a first and a second locations.

Combination of Anderson with either Schleifer (A) or Schleifer (B) would not suggest to one of skill in the art to perform the steps of contacting of blocked nucleoside monomers and the subsequent oxidation and displacement of blocking fluid more than once with the substrate of an addressable array because the addition of monomers have already been accomplished on the CPG support and the polymers cleaved. As such, the combination of these references would not suggest one of skill in the art to carry out the Applicants' claimed invention.

Since Claim 1 and its dependents are related to *in situ* fabrication of addressable arrays, in which the steps of contacting, oxidation, displacement of deblocking fluids (a, b, c, d) are performed again (e, f, g, h) on the substrate with at least a first and second locations, the claimed invention is different from the teachings of the cited references. Moreover, as admitted by the Examiner, the combination of the cited references would result in a method where in the addressable array is produced by using pre-synthesized polymers cleaved off CPG. As such, Anderson along with either Schleifer (A) or Schleifer (B) cannot teach or suggest the claimed invention. The Applicants, thus, respectfully request that this rejection be withdrawn.

Claim Rejections - 35 USC § 103 Anderson, Schleifer, Schleifer, and Blanchard

Claim 16 is rejected under 35 U.S.C. § 103(a) as allegedly obvious over Anderson et al. (US 5186824), in view of Schleifer et al. (A) (US 6077674) and Schleifer et al. (B) (US 6309828), and further in view of Blanchard (US 6384210). The Applicants respectfully traverse this rejection.

As noted above, a *prima facie* case of obviousness requires a finding that prior art includes all the elements with only the difference being the actual combination. In making this rejection, the Examiner asserts that Anderson along with either Schleifer (A) or Schleifer (B) teaches all the steps of Claim 1 but does not teach pulse-jet addition in oligonucleotide synthesis. The Examiner then cited Blanchard in an attempt to remedy this deficiency.

As discussed above, the Applicants submit that the combination of Anderson and Schleifer (A) or Schleifer (B) fails to teach or suggest all the elements of the claimed invention. Claim 1 is drawn to an *in situ* fabrication process of an addressable array and none of the references teach and suggest such process. For example, one of the missing elements is step (e) of Claim 1, reciting "contacting blocked nucleoside monomers to at least said first location and said second location of said substrate surface [...] to produce a substrate surface displaying covalently bound blocked nucleotides," with "said substrate surface" referring to the substrate surface of step (a).

Moreover, combining Anderson with either Schleifer (A) or Schleifer (B) would lead one of skill in the art to arrive at a process in which polymers are pre-synthesized on CPG supports and then cleaved off before contacting an addressable array. Since this is not the Applicants' claimed invention, the combination of these references cannot suggest Claim 1 and its dependents.

Blanchard is solely cited for its teaching of microdroplets designed to be delivered by inkjet technology. As such, Blanchard cannot remedy the deficiency of Anderson, Schleifer (A), and Schleifer (B). As a dependent claim of Claim 1, Claim 16 contains all the limitations of Claim 1 so it cannot be rendered obvious by the cited references.

Claim Rejections - 35 USC § 102 Bass

Claims 1, 16, and 28 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bass (US 6420180). The Applicants respectfully traverse this rejection.

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Claim 1 and its dependents are drawn to an *in situ* fabrication process in which two of the steps involve removal of deblocking fluid. The Applicants submit that Bass fails to disclose each and every element of the claimed invention. For example, Bass does not disclose the displacement steps (d and h) of Claim 1, reciting "removing deblocking fluid from the deblocked surface by displacing the deblocking fluid with a wash fluid."

In making this rejection, the Examiner points to col. 1, line 55 to col. 2, lines 9, and lines 28-34 as allegedly anticipating Claim 1. This passage in Bass merely lists the steps of an *in situ* fabrication method, including coupling, blocking, oxidizing, and removing the protecting group. However, the step of Claim 1 reciting "removing deblocking fluid [...] by displacing the deblocking fluid with a wash fluid" is missing in Bass. Nowhere does Bass provide these steps of Claim 1.

Since steps (d) and (h) of Claim 1 are absent in Bass, Bass cannot anticipate Claims 1, 16, and 28. As such, the Applicants respectfully request the withdrawal of this rejection.

Claim Rejections - 35 USC § 103 Bass and Anderson

Claims 2 and 4-15 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bass (US 6420180) in view of Anderson et al. (US 5186824). The Applicants respectfully traverse this rejection.

Claims 2 and 4-15 are further describe the *in situ* fabrication process of Claim 1. They are also ultimately dependent on Claim 1 and thus contain all the limitations of Claim 1.

In making this rejection, the Examiner asserts that Bass's teaching of fabricating an addressable array in combination with Anderson's teaching of fluid displacement renders the claims obvious. The Applicants submit that if the Examiner were to modify Bass along with Anderson to read onto the Applicants' claimed invention, the proposed combination would either change the principle of operation of the methods taught by the references or render them inoperable. Under current law, such logic cannot be used to establish a *prima facie* case of obviousness.

It is well established that a reference cannot render an invention obvious

if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified...¹

or

if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose.²

As noted above, Bass teaches *in situ* fabrication of an addressable array. Anderson teaches an enclosed rotor that permits separations involving phases of different density. In Fig. 1 and 2A-2D pointed out by the Examiner in Anderson, solid phase reactions performed on solid support such as CPG are retained in suspension inside Anderson's rotor during fluid displacement. If one were to combine the teachings of Bass and that of Anderson's, one would end up having an addressable array inside the enclosed rotor. Since a glass bead is not an addressable array nor can an addressable array exist in suspension, it would render either Bass's method or Anderson's method inoperable. This combination would also render Bass's array

¹ *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI

² *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

inoperable for the following reason. As the Examiner points out in Bass's column 2, lines 28-34, "different monomers may be deposited at different addresses on the substrate during any one cycle." Such deposition during fabrication would be inoperable if the substrate were to be enclosed in Anderson's rotor.

Furthermore, if one were to modify the teachings of Bass or Anderson to comport with the Applicants' claimed invention, the proposed modification would change the principle of operation of the cited references. An operable modification would not contain the element of fluid displacement in a rotor or column taught by Anderson since it would be inoperable as described above. A *prima facie* case of obviousness cannot be established by completely eliminating the principle operation of Anderson.

In view of the foregoing discussion, the combination of Bass and Anderson cannot render the rejected claims obvious because the propose modification would either change the principle of operation or render the methods taught inoperable. As such, the combination of these cited references cannot be used to establish a *prima facie* case of obviousness. Thus, the Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the amendments and remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

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